SUPPLEMENTARY DATA FOR:

Selective and potent agonists for estrogen receptor beta derived from molecular refinements of salicylaldoximes

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Chemistry

Commercially available chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification, with the exception of **3**, which was prepared as previously reported [S1]. NMR spectra were obtained with a Varian Gemini 200 MHz spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced from solvent references. Electron impact (EI, 70 eV) mass spectra were obtained on a ThermoQuest Finningan (TRACE GCQ plus MARCA) mass spectrometer. Melting points were measured with a Kofler apparatus. Purity was routinely measured by HPLC on a Waters SunFire RP 18 (3.0 x 150 mm, 5 μm) column (Waters, Milford, MA, www.waters.com) using a Beckmann SystemGold instrument consisting of a chromatography 125 Solvent Module and a 166 UV Detector. Mobile phases: 10 mM ammonium acetate in Millipore purified water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes and held at 80% for 10 min; flow rate was 0.7 mL/min and injection volume was 30 μL; retention times (HPLC, t_R) are given in minutes. HPLC purity of final compounds (**2b**-**g**) was determined by monitoring at 254 and 300 nm and was found in the range 96-99%. Chromatographic separations were performed on silica gel columns by flash (Kieselgel 40, 0.040–0.063 mm; Merck) or gravity column (Kieselgel 60, 0.063–0.200 mm; Merck) chromatography. Reactions were followed by thin-layer chromatography (TLC) on Merck aluminum silica gel (60 F_{254}) sheets that were visualized under a UV lamp. Evaporation was performed in vacuo (rotating evaporator). Sodium sulfate was always used as the drying agent. Microwave assisted reaction were run in a CEM or Biotage microwave synthesizer.

*General procedure for the synthesis of O-allyl-substituted-phenols **7e**,**f***

A solution of the appropriate phenol **6e**,**f** (14.0 mmol) in acetonitrile (40 mL) was treated with K_2CO_3 (2.3 g, 17 mmol). The mixture was then heated to 80 °C and treated, dropwise, with a solution of allyl bromide (2.7 g, 22 mmol) in acetonitrile (9.5 mL). Heating was continued for 3 h and then the mixture was left under stirring at the same temperature overnight. After cooling to room temperature (RT), the reaction mixture was filtered by suction, with repeated washing of the filter with diethyl ether, and the filtrate was concentrated under vacuum to afford a crude residue that was purified by column chromatography over silica gel

*2-(Allyloxy)-4-chloro-1-methylbenzene (**7e**)*

Elution with *n*-hexane/EtOAc 7:3, (R_f = 0.59) afforded pure **7e** as an oil (98% yield); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.20 (s, 3H, CH_3), 4.52 (dt, 2H, *J* = 4.9, 1.5 Hz, –CH_2O–), 5.30 (dq, 1H, *J* = 10.4, 1.5 Hz, H3'$_{anti}$), 5.43 (dq, 1H, *J* = 17.2, 1.6 Hz, H3'$_{syn}$), 6.06 (ddt, 1H, *J* = 17.3, 10.5, 4.9 Hz, H2'), 6.79 (d, 1H, *J* = 1.8 Hz, H3), 6.84 (dd, 1H, *J* = 7.9, 2.0 Hz, H5), 7.05 (d, 1H, *J* = 7.9 Hz, H6).

*2-(Allyloxy)-1-chloro-4-methylbenzene (**7f**)*

Elution with *n*-hexane (R_f = 0.68) afforded pure **7f** (99% yield) as an oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.37 (s, 3H, CH_3), 4.59 (dt, 2H, *J* = 5.1, 1.6 Hz, –CH_2O–), 5.29 (dq, 1H, *J* = 10.5, 1.5 Hz, H3'$_{anti}$), 5.47 (dq, 1H, *J* = 17.2, 1.6 Hz, H3'$_{syn}$), 6.13 (ddt, 1H, *J* = 17.2, 10.6, 5.1 Hz, H2'), 6.68-6.75 (m, 2H, H3, H5), 7.23 (d, 1H, *J* = 7.7 Hz, H6).

*General procedure for the transposition of O-allyl-substituted-phenols **7e**,**f** generating o-allylphenols **8e**,**f***

The appropriate *O*-allylphenol **7e**,**f** (6.02 mmol) was heated as such under nitrogen in a sealed vial to 210 °C overnight. After cooling to room temperature, the crude product was purified by flash chromatography over silica gel.

*2-Allyl-3-chloro-6-methylphenol (**8e**)*

Elution with *n*-hexane (R_f = 0.15) afforded pure **8e** (50% yield) as an oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.22 (s, 3H, CH_3), 3.61 (dt, 2H, *J* = 6.0, 1.6 Hz. CH_2), 5.06 (*exchangeable* s, 1H, OH), 5.09-5.21 (m, 2H, H3'$_{anti}$, H3'$_{syn}$), 5.98 (ddt, 1H, *J* = 17.7, 9.6, 6.0 Hz, H2'), 6.90 (d, 1H, *J* = 8.1 Hz, H4), 6.96 (d, 1H, *J* = 8.3 Hz, H5).

*2-Allyl-6-chloro-3-methylphenol (**8f**)*

Elution with *n*-hexane/EtOAc 9:1 (R_f = 0.35) afforded pure **8f** (56% yield) as an oil; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.26 (s, 3H, CH_3), 3.46 (dt, 2H, *J* = 5.9, 1.6 Hz, CH_2), 4.90-5.06 (m, 2H, H3'$_{anti}$, H3'$_{syn}$), 5.58 (*exchangeable* s, 1H, OH), 5.84-6.04 (m, 1H, H2'), 6.70 (d, 1H, *J* = 8.2 Hz, H4), 7.10 (d, 1H, *J* = 8.2 Hz, H5).

*General procedure for the synthesis of β-methylstyrene derivatives **9e**,**f***

The appropriate *o*-allylphenol **8e**,**f** (2.74 mmol) was dissolved in dimethyl sulfoxide (5 mL) and treated with potassium *tert*-butoxide (1.0 g, 8.9 mmol). The resulting suspension was heated to 55 °C for 4 h. After cooling to room temperature, the mixture was neutralized with a saturated aqueous ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with brine, dried, and concentrated under vacuum. The crude product was purified by flash chromatography over silica gel.

*(E)-3-Chloro-6-methyl-2-(prop-1-enyl)phenol (**9e**)*

Elution with *n*-hexane/EtOAc 9:1 (R_f = 0.44) afforded **9e** (85% yield) as a colorless solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.99 (dd, 3H, *J* = 6.4, 1.6 Hz, 3'-CH_3), 2.22 (s, 3H, 6-CH_3), 5.74 (*exchangeable* s, 1H, OH), 6.09 (dq, 1H, *J* = 16.5, 6.4 Hz, H2'), 6.41 (dq, 1H, *J* = 16.4, 1.6 Hz, H1'), 6.85 (d, 1H, *J* = 8.1 Hz, H4), 6.93 (d, 1H, *J* = 8.2 Hz, H5). Mp: 51-53 °C.

*(E)-6-Chloro-3-methyl-2-(prop-1-enyl)phenol (**9f**)*

Elution with *n*-hexane (R_f = 0.12) afforded pure **9f** (78% yield) as a colorless solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.96 (dd, 3H, *J* = 6.0, 0.8 Hz, 3'-CH_3), 2.27 (s, 3H, 6-CH_3), 5.78 (*exchangeable* s, 1H, OH), 6.20 (dq, 1H, *J* = 16.1, 6.0 Hz, H2'), 6.37 (dq, 1H, *J* = 16.4, 0.6 Hz, H1'), 6.69 (d, 1H, *J* = 8.2 Hz, H4), 7.08 (d, 1H, *J* = 8.2 Hz, H5). Mp: 53-55 °C.

*General procedure for the synthesis of salicylaldehydes **10e**,**f***

A solution of the appropriate styrene derivative **9e**,**f** (1.09 mmol) in dioxane (11 mL) was treated with 5 mL of water, 530 mg of sodium periodate (2.48 mmol), and 0.4 mL of a 2.5% solution of osmium tetroxide in *tert*-butyl alcohol (0.03 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was then diluted with water and extracted with chloroform. The organic phase was washed with aqueous sodium thiosulfate, dried, and concentrated to afford a crude residue that was purified by flash chromatography over silica gel.

*6-Chloro-2-hydroxy-3-methylbenzaldehyde (**10e**)*

Elution with *n*-hexane/ethyl acetate 9:1 (R_f = 0.50) afforded **10e** (53% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.22 (s, 3H, CH_3), 6.86 (d, 1H, *J* = 8.0 Hz, H5), 7.27 (d, 1H, *J* = 7.8 Hz, H4), 10.40 (s, 1H, CHO), 12.20 (*exchangeable* s, 1H, OH). Mp: 37-39 °C.

*3-Chloro-2-hydroxy-6-methylbenzaldehyde (**10f**)*

Elution with *n*-hexane (R_f = 0.38) afforded pure **10f** (73% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.60 (s, 3H, CH_3), 6.69 (d, 1H, *J* = 8.6 Hz, H5), 7.48 (d, 1H, *J* = 8.8 Hz, H4), 10.29 (s, 1H, CHO), 12.41 (*exchangeable* s, 1H, OH). Mp: 50-52 °C.

*General procedure for the synthesis of bromo-substituted salicylaldehydes **11e**,**f***

The appropriate salicylaldehyde **10e**,**f** (0.58 mmol) was dissolved in acetic acid, and bromine (0.1 g, 0.6 mmoli) was added. The mixture was stirred at room temperature for 48 h. The mixture was neutralized with a saturated aqueous sodium thiosulfate solution and extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated under vacuum. The crude product was purified by flash chromatography over silica gel.

*3-Bromo-2-chloro-6-hydroxy-5-methylbenzaldehyde (**11e**)*

Elution with *n*-hexane/EtOAc 9:1 (R_f = 0.42) afforded **11e** (48% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.22 (s, 3H, CH_3), 7.58 (s, 1H, H4), 10.41 (s, 1H, CHO), 12.32 (*exchangeable* s, 1H, OH). Mp: 38-40 °C.

*3-Bromo-5-chloro-6-hydroxy-2-methylbenzaldehyde (**11f**)*

Elution with *n*-hexane/EtOAc 9:1 afforded pure **11f** (43% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.68 (s, 3H, CH_3), 7.79 (s, 1H, H4), 10.35 (s, 1H, CHO). Mp: 55-57 °C.

*General procedure for the synthesis of o-methoxybenzaldehydes **12e**,**f***

The appropriate salicylaldehyde **11e**,**f** (0.58 mmol) was dissolved in acetone and treated with 160 mg of potassium carbonate (1.16 mmol). The mixture was treated, dropwise, with iodomethane (0.17 g, 1.2 mmoli), and stirred at room temperature overnight. Part of the solvent was removed under vacuum, and

the mixture was diluted with water and extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by flash chromatography over silica gel.

*3-Bromo-2-chloro-6-methoxy-5-methylbenzaldehyde (**12e**)*

Elution with *n*-hexane/EtOAc 9:1 (R_f = 0.35) afforded **12e** (65% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.28 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.66 (s, 1H, H4), 10.38 (s, 1H, CHO). Mp: 40-42 °C.

*3-Bromo-5-chloro-6-methoxy-2-methylbenzaldehyde (**12f**)*

Elution with *n*-hexane/EtOAc 9:1 (R_f = 0.44) afforded pure **12f** (74% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.60 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.81 (s, 1H, H4), 10.44 (s, 1H, CHO). Mp: 53-55 °C.

*Synthesis of 6-methoxy-2,3-bis-(4-methoxyphenyl)benzaldehyde (**4b**)*

A solution of $Pd(OAc)_2$ (3.1 mg, 0.014 mmol) and triphenylphosphine (18.4 mg, 0.070 mmol) in ethanol (1.0 mL) and toluene (1.0 mL) was stirred at RT under nitrogen for 10 min. After that period, compound **3** [18] (115 mg, 0.461 mmol), an aqueous solution of Na_2CO_3 (1.0 mL, 2 M), and 4-methoxyphenylboronic acid (112 mg, 0.74 mmol) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under nitrogen overnight. After being cooled to RT, the mixture was diluted with water and extracted with EtOAc. The combined organic phase were dried and concentrated. The crude product was then submitted as such to a second cycle of cross-coupling, by repeating the same procedure described above. Finally, the crude mixture was purified by flash chromatography over silica gel (*n*-hexane/ EtOAc 8:2, R_f = 0.14) to yield **4b** as a yellow solid (22% yield, 2 steps). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.71 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.4 Hz, ArH), 6.76 (AA'XX', 2H, J_{AX} = 8.6 Hz,

$J_{AA'/XX'}$ = 2.5 Hz, ArH), 6.91 (AA'XX', 2H, J_{AX} = 8.5 Hz, $J_{AA'/XX'}$ = 2.6 Hz, ArH), 6.95 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.4 Hz, ArH), 7.04 (d, 1H, J = 8.8 Hz, H5), 7.50 (d, 1H, J = 8.6 Hz, H4), 9.85 (s, 1H, CHO). Mp: 44-45 °C.

*General procedure for the synthesis of aryl-substituted o-methoxybenzaldehydes **4e–g***

A solution of $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and triphenylphosphine (16.9 mg, 0.064 mmol) in ethanol (1.0 mL) and toluene (1.0 mL) was stirred at RT under nitrogen for 10 min. After that period, the appropriate bromo-aryl precursor **12e**, or **12f** (0.43 mmol), an aqueous solution of Na_2CO_3 (1.0 mL, 2 M), and the appropriate arylboronic acid (1.2 equiv) were sequentially added. The resulting mixture was heated at 100 °C in a sealed vial under nitrogen overnight. After being cooled to RT, the mixture was diluted with water and extracted with EtOAc. The combined organic phase were dried and concentrated. The crude product was purified by flash chromatography over silica gel.

*2-Chloro-4,4'-dimethoxy-5-methylbiphenyl-3-carbaldehyde (**4e**)*

Elution with *n*-hexane/EtOAc 95:5 (R_f = 0.15) afforded pure **4e** (75% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.97 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.5 Hz, H3', H5'), 7.31 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.6 Hz, H2', H6'), 7.35 (s, 1H, H6), 10.52 (s, 1H, CHO). Mp: 44-46 °C.

*5-Chloro-4,4'-dimethoxy-2-methylbiphenyl-3-carbaldehyde (**4f**)*

Elution with *n*-hexane/EtOAc 95:5 (R_f = 0.25) afforded pure **4f** (88% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.39 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.95 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.3 Hz, H3', H5'), 7.16 (AA'XX', 2H, J_{AX} = 8.5 Hz, $J_{AA'/XX'}$ = 2.5 Hz, H2', H6'), 7.47 (s, 1H, H6), 10.58 (s, 1H, CHO). Mp: 50-52 °C.

*5-Chloro-3'-fluoro-4,4'-dimethoxy-2-methylbiphenyl-3-carbaldehyde (**4g**)*

Elution with *n*-hexane/EtOAc 95:5 (R_f = 0.30) afforded pure **4g** (54% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.39 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.91-7.06 (m, 3H, H2', H5', H6'), 7.45 (s, 1H, H6), 10.57 (s, 1H, CHO). Mp: 50-52 °C.

*Synthesis of 6-Hydroxy-2,3-bis-(4-hydroxyphenyl)benzaldehyde (**5b**)*

A solution of **4b** (26 mg, 0.075 mmol) in anhydrous dichloromethane (1 mL) was cooled to –78 °C and treated dropwise with a solution of BBr_3 in dichloromethane (0.7 mL, 1M), and the resulting solution was stirred at the same temperature for 5 min and at 0 °C for 1 h. The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was dried and concentrated. The crude product was purified by flash chromatography over silica gel (*n*-hexane/EtOAc 7:3, R_f = 0.14) to yield pure **5b** (90% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 4.80 (*exchangeable* bs, 1H, OH), 5.00 (*exchangeable* bs, 1H, OH), 6.64 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz, ArH), 6.74 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.5 Hz, ArH), 6.86 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz, ArH), 6.97 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.4 Hz, ArH), 7.02 (d, 1H, J = 8.6 Hz, H5), 7.52 (d, 1H, J = 8.6 Hz, H4), 9.70 (s, 1H, CHO), 12.01 (*exchangeable* bs, 1H, OH). Mp: 45-46 °C.

*General procedure for the O-demethylation of **4e–g** generating salicylaldehydes **5e–g***

A solution of the appropriate methoxy-substituted aldehyde **4e**–**g** (0.12 mmol) in anhydrous dichloromethane (1.5 mL) was cooled to –78 °C and treated dropwise with a solution of BBr_3 in dichloromethane (0.7 mL, 1M), and the resulting solution was stirred at the same temperature for 5 min and at 0 °C for 1 h. The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was dried and concentrated. The crude product was purified by flash chromatography over silica gel.

*2-Chloro-4,4'-dihydroxy-5-methylbiphenyl-3-carbaldehyde (**5e**)*

Elution with *n*-hexane/EtOAc 8:2 (R_f = 0.24) afforded pure **5e** (43% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.25 (s, 3H, CH_3), 5.05 (*exchangeable* bs, 1H, OH), 6.90 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.4 Hz, H3', H5'), 7.25 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.4 Hz, H2', H6'), 7.33 (s, 1H, H6), 10.51 (s, 1H, CHO), 12.39 (*exchangeable* s, 1H, OH). Mp: 48-50 °C.

*5-Chloro-4,4'-dihydroxy-2-methylbiphenyl-3-carbaldehyde (**5f**)*

Elution with *n*-hexane/EtOAc 7:3 (R_f = 0.27) afforded pure **5f** (48% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.48 (s, 3H, CH_3), 6.89 (AA'XX', 2H, J_{AX} = 8.4 Hz, $J_{AA'/XX'}$ = 2.4 Hz, H3', H5'), 7.11 (AA'XX', 2H, J_{AX} = 8.4 Hz, $J_{AA'/XX'}$ = 2.5 Hz, H2', H6'), 7.49 (s, 1H, H6), 10.40 (s, 1H, CHO). Mp: 57-59 °C.

*5-Chloro-3'-fluoro-4,4'-dihydroxy-2-methylbiphenyl-3-carbaldehyde (**5g**)*

Elution with *n*-hexane/EtOAc 7:3 (R_f = 0.30) afforded pure **5g** (55% yield) as a yellow solid; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.49 (s, 3H, CH_3), 6.87-7.10 (m, 3H, H2', H5', H6'), 7.47 (s, 1H, H6), 10.40 (s, 1H, CHO). Mp: 57-59 °C.

*General procedure for the synthesis of final salicylaldoximes **2b,e–g***

A solution of the appropriate aldehyde **5b,e**-**g** (1.0 mmol) in ethanol (15 mL) was treated with a solution of hydroxylamine hydrochloride (140 mg, 2.02 mmol) in water (3.5 mL), and the mixture was heated to 50 °C for up to 5h. After being cooled to RT, part of the solvent was removed under vacuum, and the mixture was diluted with water and extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography over silica gel using the indicated *n*-hexane/EtOAc mixtures. Compound HPLC purity was determined by monitoring at 254

and 300 nm under conditions reported above and was found in the range 96-99% with the retention times (t_R) of the only or predominant peak indicated for each compound.

*(E)-6-Hydroxy-2,3-bis-(4-hydroxyphenyl)benzaldehyde oxime (**2b**)*

Elution with *n*-hexane/EtOAc 3:7 (R_f = 0.39) afforded pure **2b** (64% yield) as a white solid; ^{1}H NMR (CD_3OD) δ (ppm): 6.54 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.5 Hz, ArH), 6.69 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.3 Hz, ArH), 6.80 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.6 Hz, ArH), 6.83 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.4 Hz, ArH), 6.92 (d, 1H, J = 8.6 Hz, H5), 7.22 (d, 1H, J = 8.4 Hz, H4), 7.94 (s, 1H, –CH=N–). ^{13}C NMR (CD_3OD) δ (ppm): 115.30, 115.64, 116.15, 116.55, 130.61, 131.87, 133.18, 133.23, 134.09, 134.67, 142.66, 152.15, 156.45, 157.48, 157.94. MS *m/z* 321 (M^+, 100), 303 (M^+ –H_2O, 29). Mp: 170-172 °C. HPLC, t_R 9.6 min.

*(E)-2-Chloro-4,4'-dihydroxy-5-methylbiphenyl-3-carbaldehyde oxime (**2e**)*

Elution with *n*-hexane/EtOAc 8:2 (R_f = 0.15) afforded pure **2e** (72% yield) as a white solid; ^{1}H NMR (acetone-d_6) δ (ppm): 2.27 (s, 3H, CH_3), 6.90 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.6 Hz, H3', H5'), 7.41 (s, 1H, H6), 7.46 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz, H2', H6'), 8.37 (*exchangeable* s, 1H, OH), 8.42 (s, 1H, –CH=N–), 10.28 (*exchangeable* s, 1H, OH), 10.70 (*exchangeable* s, 1H, OH). ^{13}C NMR (acetone-d_6) δ (ppm): 15.95, 116.47, 117.53, 126.25, 126.96, 128.27, 130.77, 132.64, 133.08, 153.20, 155.29, 157.46. MS *m/z* 277 (M^+, 5), 260 (M^+ –OH, 10), 243 (M^+ –2OH, 100), 225 (M^+ –2OH –H_2O, 56). Mp: 137-138 °C. HPLC, t_R 10.1 min.

*(E)-5-Chloro-4,4'-dihydroxy-2-methylbiphenyl-3-carbaldehyde oxime (**2f**)*

Elution with *n*-hexane/EtOAc 8:2 (R_f = 0.18) afforded pure **2f** (79% yield) as a white solid; ^{1}H NMR (acetone-d_6) δ (ppm): 2.32 (s, 3H, CH_3), 6.91 (AA'XX', 2H, J_{AX} = 8.8 Hz, $J_{AA'/XX'}$ = 2.5 Hz, H3', H5'), 7.13 (AA'XX', 2H, J_{AX} = 8.6 Hz, $J_{AA'/XX'}$ = 2.4 Hz, H2', H6'), 7.21 (s, 1H, H6), 8.47 (*exchangeable* s,

1H, OH), 8.70 (s, 1H, –CH=N–), 11.01 (*exchangeable* s, 1H, OH), 11.37 (*exchangeable* s, 1H, OH). ^{13}C NMR (acetone-d_6) δ (ppm): 16.84, 115.96, 117.48, 118.88, 131.44, 132.57, 133.03, 135.10, 135.61, 150.91, 153.56, 157.52. MS *m/z* 277 (M^+, 100), 260 (M^+ –OH, 80), 225 (M^+ –2OH –H_2O, 51). Mp: 139-140 °C. HPLC, t_R 10.5 min.

*(E)-5-Chloro-3'-fluoro-4,4'-dihydroxy-2-methylbiphenyl-3-carbaldehyde oxime (**2g**)*

Elution with *n*-hexane/EtOAc 8:2 (R_f = 0.18) afforded pure **2f** (79% yield) as a white solid; ^{1}H NMR (acetone-d_6) δ (ppm): 2.33 (s, 3H, CH_3), 6.94 (ddd, 1H, *J* = 8.3, 2.0, 0.7 Hz, H5'), 7.02-7.11 (m, 2H, H2', H6'), 7.23 (s, 1H, H6), 8.70 (s, 1H, –CH=N–), 8.80 (*exchangeable* bs, 1H, OH), 11.10 (*exchangeable* bs, 1H, OH), 11.40 (*exchangeable* bs, 1H, OH). ^{13}C NMR (acetone-d_6) δ (ppm): 16.77, 117.46, 117.75, 118.23 (d, *J* = 11.9 Hz), 118.66 (d, *J* = 25.6 Hz), 126.64 (d, *J* = 2.7 Hz), 132.90, 133.35, 135.10, 137.98 (d, *J* = 38.4 Hz), 144.86 (d, *J* = 12.8 Hz), 150.72, 151.75 (d, *J* = 240.8 Hz), 153.78. MS *m/z* 295 (M^+, 97), 278 (M^+ –OH, 100). Mp: 155-156 °C. HPLC, t_R 10.9 min.

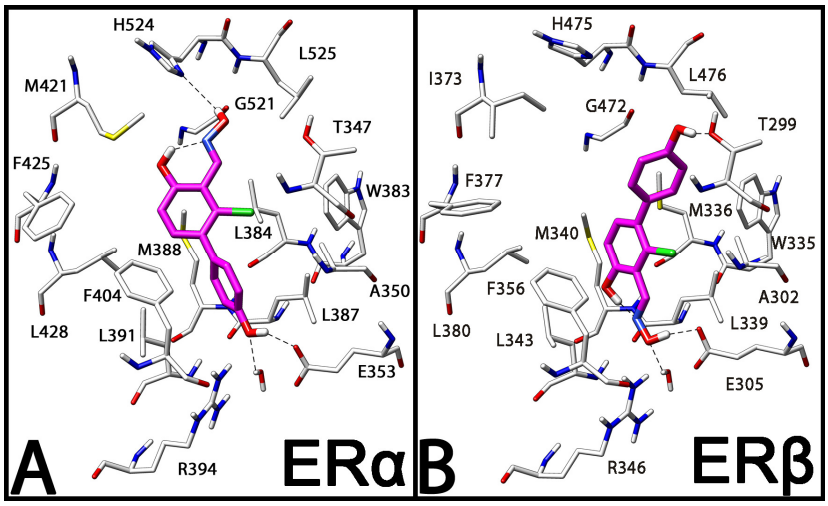

Figure S1. Docking analysis of compound **2c** into ERα and ERβ

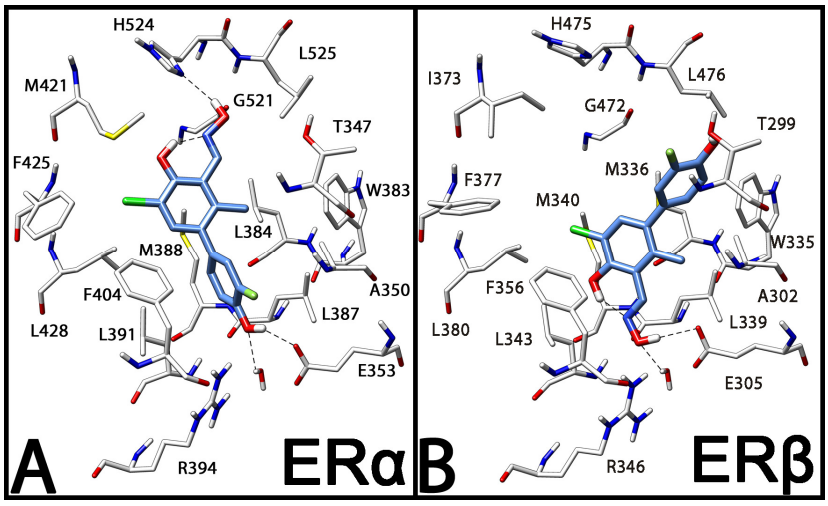

Figure S2. Docking analysis of compound **2g** into ERα and ERβ

References

[S1] B. Akermark, Acta Chem. Scand. 24 (1970), 1459–1460.